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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,220	SHEN, CHE-KUN JAMES	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 21-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 21-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/1/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 12/01/03 has been acknowledged.

Claims 11-20 are canceled.

Claims 21-31 are newly filed.

Claim 2 is amended.

Claims 1-10 and 21-31 are pending and are examined in this office action.

*Applicants are required to follow Amendment Practice under revised **37 CFR §1.121**. The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 23-30 has been renumbered 24-31.

Double Patenting

Claims 1-10 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of copending Application No. 09/961,563. The applicants requested to hold this rejection in abeyance until such time as there is an indication of otherwise allowable subject matter.

Claim Rejections - 35 USC § 112

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter issues). The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly submitted claim 22 is drawn to and isolated cell and progeny thereof, wherein the cell is form an animal selected from the group consisting of pig, rat, cow, rabbit, goat, guinea pig, prarie baboon, squirrel, monkey, chimpanzee, frog, toad, chicken, turkey and sheep. The applicant fails to point out where is the support for claimed subject matter in the instant specification. The instant specification fails to disclose an isolated cell obtained form a rat, cow, rabbit, goat, guinea pig, prarie baboon, squirrel, monkey, chimpanzee, frog, toad, chicken, turkey and sheep.

Claims 1-10 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enabling for a transgenic pig (HS40(mt)-ζ597hGH), whose somatic and germ line cells contain a transgene comprising a transcriptional start site, the human ζ-globin promoter operably linked to a transcriptional start site and a mutant human HS-40 enhancer (SEQ ID NO:1) operably linked to the ζ-globin promoter which drives the expression of human growth hormone in erythroblasts, does not reasonably provide enablement for any and all transgenic non-mouse non-human animals wherein the transgene encodes a transcriptional start site and an enhancer operably linked to any and all kind of promoter that leads to expression of transgene transcripts in all type of cells in the transgenic animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons of record as set forth in the office action mailed on 12/01/03.

Nature Of Invention:

Invention relates to transgenic animals.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of instant claim encompasses any and all non-mouse non-human transgenic animals (insects, fish reptiles, birds, whales, horses and various primates), whose somatic and germ line calls contain a transgene (as claimed). The scope of transgene encompasses the presence of any and all promoters operatively linked to nucleotide sequences encoding any and all polypeptides of interest. In addition the scope of invention as claimed encompasses the expression of transgene transcripts in at least one type of cells. The specification as filed teaches a DNA-construct that encodes a transgene comprising a transcriptional start site, the human ζ-globin promoter operably linked to a transcriptional start site and a mutant human HS-40 enhancer operably linked to the ζ-globin promoter, which drives the expression of human growth hormone. In addition, the specification discloses a transgenic pig (HS40(mt)-ζ597hGH) that express human growth hormone in the blood (spec page 19; page pages 24-26, table-2, table-3, table-4). Besides a transgenic pig (HS40(mt)-ζ597hGH) that expresses hGH in the blood, the instant specification fails to disclose any other non-mouse non-human transgenic animal (rat, cow, rabbit, goat, guinea pig, baboon, squirrel, monkey, chimpanzee, frog, toad chicken turkey and sheep) encoding the transgene (as claimed), wherein the transgene encodes any and all polypeptides of interest.

State Of Art And Predictability:

The *state of transgenic art* at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. (Wood. Comp. Med. 50(1): 12-15, 2000, see page12). The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These epigenetic

effects can dramatically alter the observed phenotype and therefore can influence or later the conclusions drawn form the transgenic or knockout models (Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, see page 1425).

The transgene expression and physiological consequences of transgene products in non-mouse mammals are not always accurately predicted among various species of mammals (Wall RJ Theriogenology 45:57-68, 1996). Transgene efficiency is low, and range from 1% in farm animals (cattle, sheep, pigs) to 3% in laboratory animals like rabbits, mice and rats (Wall, see page 61). Furthermore, the lack of understanding of essential genetic control elements make it difficult to predict the behavior of a transgene in any and all animals because the expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene (Wall, page 61-62). The cis-acting elements of one species may interact with different transactivating factors in other species. For example, the introduction of human growth hormone transgene in mice results in mammoth mouse phenotype, where as expression of the same transgene in pig results in premature death of transgenic pigs. (Pursel VG et al J. Reprod Fert. Sup 40: 235-245 1990, see page 235, para.1). Furthermore, many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, for example are the important factors that govern the expression of a transgene. (Kappel et al. Current Opinion in Biotechnology 3:558-553 1992; see page 550, col.1, para. 3-4, page 548, col.2 para.2). In instant case considering the limited disclosure wherein a transgenic pig has been made by using (HS40(mt)-ζ597hGH) transgene construct, it is highly unpredictable that the transgene construct other than HS40(mt)-ζ597hGH would certainly lead to development of mature transgenic pigs that express hGH. In addition it is highly

unpredictable that a transgene construct comprising a mammalian ζ-globin promoter operably linked to a mammalian erythroid specific enhancer region would results in the tissue specific expression of the transgene product in non-mammalian animals like frog, toad, chicken and turkey.

Response to arguments

The applicant argues that a recent review by Wall (2001), suggest that once microinjection skills are perfected there are only a few parameters one needs to be concerned about to successfully produce transgenic animals. Furthermore, a low efficiency of transgene integration does not in and of itself indicate that the making of transgenic animals is not enabled. The applicant argues that Wall (2001) indicates that the efficiency is ~1 %, i.e., out of one hundred attempts, one transgenic animal is obtained. Thus, all one of skill in the art needs to do is transfect approximately one hundred embryos and they will get approximately one transgenic animal and such an experimentation is not undue. The applicant argues that Dr. Shen Declaration indicates generation of transgenic animals was routine in the art as of filing the application. Even though low efficiency was expected it was standard practice to generate hundreds of injected oocytes and then screen for offspring that express the transgene. The applicant argues that art has demonstrated that numerous position independent elements are effective in cross-species experimentation. The applicant argues that transgenic mice and pigs with HS-40 enhancer elements have been generated in their lab. The applicant argues that there is abundant evidence that elements that generate position independent expression are functional across species.

However, this is found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). The scope of invention as claimed encompasses any and all non-mouse non-human transgenic animals (insects, fish reptiles, birds, whales, horses and various primates), whose somatic and germ line calls contain a transgene (as claimed). Furthermore, the scope of transgene encompasses the presence of any and all promoters operatively linked to nucleotide sequences encoding any and all polypeptides of interest.

Wall (2001) clearly teaches that making of any and all transgenic animal across the "Animal Kingdom" is highly unpredictable. Wall (2001) teaches that microinjection is a low efficiency process and there are numerous parameters that influence the efficacy or producing transgenic animals by pronuclear microinjection. For example visualization of pronuclei is species dependent and may require additional steps to remove optically opaque cytoplasmic material found in the zygotes of various species (Wall, 2001, page 211, para.2). Furthermore timing of pronuclear formation is species-dependent, ranging from about 5 h (mouse) to about 11 h (pig) after sperm penetration. The developmental timing of pronuclear formation and its DNA replication state obviously dictates when injection can be performed. For example in the case of cattle, S phase is completed in about 50% of the embryos before pronuclei can be visualized. If the poor efficiency of production was not discouraging enough, the picture looks even worse when factor regarding germline transmission and transgene expression are taken in account. Only about 70% of founders transmit their transgene to offspring and little over half of established lines express their transgene at useful levels. Therefore, if 100 offspring are born one might expect to produce between 2-15 useful founders, which further depend on the animal species and other undefined factors related to the species. Wall (2001) concludes that most would agree that poor embryo survival, low transgene integration rate and unpredictable transgene behavior are the three primary contributors to pronuclear microinjection inefficiencies. The issue of poor embryo survival, at least in the context of producing transgenic animals has received little attention. It is well-accepted fact that about 75% of the microinjected zygotes does not make it to term.

Therefore applicants argument that "all one of skill in the art needs to do is transfect approximately one hundred embryos to get one transgenic animal and such an experimentation is not undue" has been found not persuasive because Wall (2001) clearly teaches that making any and all transgenic animals is highly unpredictable (*supra).* Even though HS-40 enhancer linked to any promoter may regulate the expression of a transgene in isolated cells, the regulation of a transgene expression in a transgenic animal would be highly unpredictable, since many biochemical pathways are plastic in nature which reflects the ability of the embryo to use alternative gene when the

preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct are the important factors that govern the expression of a transgene. The cis-acting elements of one species may interact with different transactivating factors in other species. For example, the introduction of human growth hormone transgene in mice results in mammoth mouse phenotype, where as expression of the same transgene in pig results in premature death of transgenic pigs (*supra).*

Thus, in view of lack of specific guidance in the specification and considering the unpredictability in the transgenic art, the skilled artesian at the time of filing would be unable to use the invention as claimed, without an excessive and undue amount of experimentation. The quantity of experimentation required would include the functional and structural characterization of any and all transgene constructs comprising all possible combinations of any promoter(s), enhancer element(s) and any gene(s) of interest. The quantity of experimentation required would further include making of any and all kind of transgenic animals like all types of insects, fish, birds, reptiles and mammals encoding any and all types of transgene constructs. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). In instant case making various species of transgenic animals across the "Animal Kingdom" is not considered routine in the art and without sufficient guidance to a method of making a particular species the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Response to Declaration

Dr. Shen Declaration's declaration has been fully considered. Discussing Wall (2001) the declaration states that inventor's laboratory uses standard protocol for generating transgenic animals. Even though the efficiency of integration is low the

experimenter was virtually assured to obtain one or more transgenic animals selected from the live stock by injecting large number of oocytes with transgene DNA. The declaration further states that HS-40 elements when coupled with a promoter can provide position independent expression in cross-species experiments. The declaration concludes that standard protocol to other animals would only require routine experimentation to modify the protocol if any modification would be required.

However, this is found NOT persuasive because Wall (2001) clearly teaches that making of any and all transgenic animal across the "Animal Kingdom" is highly unpredictable. The microinjection is a low efficiency process and there are numerous parameters that influence the efficacy or producing transgenic animals by pronuclear microinjection. For example visualization of pronuclei is species dependent and may require additional steps to remove optically opaque cytoplasmic material found in the zygotes of various species. The developmental timing of pronuclear formation and its DNA replication state varies with selection of animal species, which obviously dictates when injection can be performed. Wall (2001) concluded that poor embryo survival rate, low transgene integration rate and unpredictable transgene behavior are the three primary contributors to pronuclear microinjection inefficiencies. Even though applicants were able to make a transgenic mice and a transgenic pig, the use protocols adapted for these animal would be highly unpredictable for the making of any and all non-mouse non-human transgenic animals like insects, fish reptiles, birds, whales, horses and various primates. Thus, in view of lack of specific guidance in the specification and considering the unpredictability in the transgenic art, the skilled artesian at the time of filing would be unable to make and use any and all non-mouse/non-human transgenic animals, without an excessive and undue amount of experimentation.

Claims 21-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention:

Invention relates to a product obtained by a method of gene therapy and/or from a transgenic animal.

Breadth Of Claims And Guidance Provided By The Inventor:

The invention as claimed is drawn to an isolated cell and progeny thereof, whose genomic DNA comprises at least one copy of a transgene comprising a transcriptional start site; a promoter operably linked to the transcriptional start site; and an enhancer (SEQ ID NO:1), wherein the cell is from an animal. The scope of invention as claimed encompasses a cell isolated form a transgenic animal or a cell transduced in-vivo. At best the specification only teaches the making a transgenic pig by microinjection of a DNA fragment into the pronucleus of an embryo. Besides isolated cells obtained form a transgenic pig the specification fails to disclose an isolated cell obtained form a transgenic cow, rabbit, goat, guinea pig, baboon, squirrel, monkey, chimpanzee, frog, toad chicken turkey and sheep. In addition the specification fails to disclose how to transduce any and all type of cells in-vivo via a method of gene therapy.

State Of Art And Predictability:

The invention as claimed encompasses a cell isolated from an animal. Therefore, the invention reads upon a cell obtained by a method of gene therapy or from a transgenic animal. The art at the time of filing clearly teaches that the gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations (Rosenberg et al, Science 287:1751, 2000, also see pages 6-10 of office action mailed on06/19/03). The instant specification fails to provide any guidance regarding how to deliver a vector via any route of administration in vivo so that one skill in the art would be able to express the transgene in a target cell of interest in-vivo. For example, the specification fails to disclose how one skill in the art would delivery the transgene to a particular blood cell type (e.g. a hematopoietic stem cell) via systemically administering a vector containing the claimed genetic construct.

Similarly, the state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment.

(Wood. Comp. Med. 50(1): 12-15, 2000, see page12). Besides a transgenic pig (HS40(mt)-ζ597hGH) that expresses hGH in the blood, the instant specification fails to disclose any other transgenic animal (rat, cow, rabbit, goat, guinea pig, baboon, squirrel, monkey, chimpanzee, frog, toad chicken turkey and sheep) encoding the claimed transgene, wherein the transgene encodes any and all polypeptides of interest. Therefore considering the unpredictably in the state of transgenic art (see issues raised in the enablement rejection of claims 1-10 above) and limited amount of guidance provided in the specification, it would require an undue amount of experimentation to exercise the invention as claimed.

However, claims drawn to "an isolated animal cell" would obviate this rejection, wherein the scope of isolated cells reads upon an isolated cell wherein the cell has been transformed in-vitro.

In addition the state of the art at the time of filing teaches that a point mutation in NE-E2/AP1 motif of HS-40 enhancer element comprising G-to-T substitution as disclosed in the nucleotide sequences of SEQ ID NO:1 (tctgagtca) reduces the expression transgene construct by 70% in isolated K562 cells (an erythroid cell line) comprising (pHS40(r-mt 1)-ζ597-GH expression vector. In addition a similar base substitution of tandemly arranged NF-E2/AP1 motifs of human β-globin locus-specific enhancer 5' HS-2 was shown to completely abolish the 5' HS-2 enhancer function (Zhang et al Mol. Cell Bio 1394: 2298-2308, 1993, page 2304 col.1, para.2). The scope of invention as claimed encompasses any and all cells isolated from any and all animals. The applicant claims are in contradiction with the state of HS-40 enhancer art, which clearly state the a point mutation in NE-E2/AP1 motif of HS-40 enhancer element comprising G-to-T substitution (tctgagtca) reduces the transgene expression. The specification fails to disclose a single working example which establishes that an isolated cell whose genome comprises an enhancer element (tctgagtca) operably linked any promoter express transcripts, wherein the level of expression is positively correlated (up-regulated) with the copy number of the transgene.

Thus, in view of lack of specific guidance in the specification and considering the state of the HS-40 enhancer art, the skilled artesian at the time of filing would be unable to use the invention as claimed, without an excessive and undue amount of experimentation. The quantity of experimentation required would include making and testing the regulation of transgene expression regulated by mutated HS-40 enhancer in any and all cells (any and all tissue types) obtained form any and all animals (insects, fish, birds, reptiles and mammals). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Thus in view of state of the art which contradicts applicants assertion it is not clear how one skill in the art would exercise the invention as claimed without further undue amount of experimentation See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sumesh Kaushal
Examiner Art Unit 1636

JEFFREY FREDMAN
PRIMARY EXAMINER